REMARKS

Status of the Claims

Claims 34-44 and 58-70 are pending herein.

The Office has objected to claim language in which the ratio of detergent to monomer is "selected." Currently, the claims use the analogous term "used," which is literally supported in paragraph [0098] of the originally filed specification.

Support for the amendment of claims 43, 58 and 60 can be found throughout the originally filed specification. See, e.g., Title, Technical Field, and paragraphs [0066], [0099] and [0102], among others.

Support for new claim 68 is found in paragraph [0028] of the originally filed specification.

Support for new claim 69 is found in paragraph [0025] of the originally filed specification.

Support for new claim 70 is found in paragraphs [0096] to [0098] and Examples 5 and 6 of the originally filed specification.

No new matter is added.

Claim Rejection under 35 U.S.C. §112, first paragraph (enablement)

Withdrawal of the previous rejection of claims 34-37, 39, 42-44 and 58-61 under the 35 U.S.C. §112, first paragraph (enablement) is noted with appreciation.

Issues pertaining Claim 34

The Office has as urged that the specification does not provide antecedent basis for the 10-90% limitation in claim 34. It is respectfully submitted that paragraph [0022] of the specification provides the requisite support.

The Office argues that the there is no support for "selecting" a ratio of detergent to polymer as claimed. Applicant disagrees and believes that support, although not in identical language, is found in paragraph [0098] of the original specification. Nonetheless, to advance prosecution of the present application toward allowance, the claims have been amended to reflect

the exact language of paragraph [0098] (i.e., a detergent to polymer ratio is "used" which yields a desired amount of detergent in bound and unbound form).

Claim Rejection under 35 U.S.C. §112, first paragraph (written description)

Claims 34-36, 39-44, 60-63, 66 and 67 were rejected under 35 U.S.C. §112, first paragraph as allegedly not complying with the written description requirement. Specifically, the Office urges that the specification as originally filed does not provide support for a limitation where the specific ratio of detergent to polymer is selected to arrive at the desired amount of detergent in bound and unbound form. This rejection is believed to be moot in view of the above claim amendments, as the claims presently recite that a ratio of detergent to polymer ratio is "used" to arrive at a desired amount of detergent in bound and unbound form. See paragraph [0098], first and second sentences

Reconsideration and withdrawal of the outstanding rejection under 35 U.S.C. §112, first paragraph are therefore respectfully requested.

Objection to the Specification

The specification is objected to as allegedly lacking antecedent basis for selecting a specific ratio of detergent to polymer that would arrive at a 10-90% detergent bound to the microparticles. With respect to "selecting" a specific ratio of detergent to polymer, this objection is believed to be moot in view of the above amendment to claims 34 and 39. With respect to the 10-90% detergent bound to the microparticles, it is respectfully submitted that paragraph [0022] of the specification provides the desired support.

Claim Rejection under 35 U.S.C. §112, second paragraph

Withdrawal of the rejection of claims 34-44 and 58-61 under 35 U.S.C. §112, second paragraph is noted with appreciation.

Claim Rejection under 35 U.S.C. 103-Levy in view of Paliard

Claims 34-44 and 58-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,395,253 to Levy et al. (Levy) in view of US 6,562,346 to Paliard et al. (Paliard). Applicant respectfully traverses this rejection and its supporting remarks.

The claimed invention relates to new methods for the production of microparticle compositions. As explained in the present application at paragraph [0011] onwards:

> The present inventors have found that adsorption of macromolecules to microparticles can be improved by ensuring that detergent is made available for forming a complex with the macromolecules at the time of adsorption. This availability can be accomplished, for example, by separately providing a quantity of detergent at the time of macromolecule adsorption or by ensuring that the process for producing the microparticles results in a product containing a substantial amount of unbound detergent.

Thus, the application teaches two different approaches for ensuring that unbound detergent is available for forming a complex with the macromolecules at the time of adsorption.

Each of the independent claims in the present application (34, 37 and 39), requires either (I) that the microparticles are subjected to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound or (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

With respect to limitation (II) above, the Office argues that while the Examples of Levy require a washing step, Section 4.2 does not. Respectfully, in Section 4.2, Levy discloses a "basic" process for making microspheres containing bioactive agents water-in-oil-in-water (W/O/W) double emulsion protocol described in Levy et al., WO96/20698; Yamamoto et al., European Patent Application EP 190,833; and Okada et. al., U.S. Pat. No. 5,480,656. The protocol set forth is merely a "brief description" of the protocols set forth in these documents. Each document, however, describes washing in conjunction with the W/O/W double emulsion protocol set forth therein. See, e.g., WO96/20698 at page 16, lines 18-20 and page 19, lines 13-14, EP 190,833 at col. 9, lines 18-20 and U.S. Patent No. 5,480,656 at col. 5, lines 48-50.

Furthermore, it is respectfully submitted that one of ordinary skill in the art would not read Section 4.2 in a manner that is decoupled from the Examples. See MPEP 2141.02.VI: A prior art reference must be considered in its entirety, i.e., as a whole, including portions that

would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

Thus, if one reads Section 4.2 in context (and not in isolation), a washing step is clearly included in the protocol described.

In this regard, it is noted that, upon reviewing Levy, one of ordinary skill in the art would have referenced Levy's procedures, as set forth in the Examples, to produce microspheres. In particular, Levy teaches a method of producing microspheres comprising forming a W/O/W emulsion, evaporating the organic solvent from the W/O/W emulsion, recovering microspheres by ultracentrifugation, and washing recovered microspheres multiple times. See, e.g., the Examples of Levy.

Moreover, nowhere in Levy is it suggested that one should ensure that the process for producing the microparticles results in a product containing the amounts of unbound and bound detergent claimed.

With respect to limitation (I) above, the Office takes the position that "centrifugation can be considered filtration." However, one of ordinary skill in the art would readily understand that centrifugation is not a filtration process. For example, *Hawley's Condensed Chemical Dictionary*, Fourteenth Edition, John Wiley & Sons, 2001, page 497 defines "filtration" as "[t]he operation of separating suspended solids from a liquid (or gas) by forcing the mixture through a porous barrier ..." Filtration includes separations at the molecular level. (See attached.) "Filtration," however, clearly does not embrace centrifugation.

Moreover, as noted above, the teachings of Levy would not have led one of ordinary skill in the art to practice a method which produces the claimed amounts of bound and unbound detergent.

In addition to ensuring that unbound detergent is made available for complex formation with macromolecules, the processes of the present invention are advantageous relative to those of Levy, *inter alia*, because they do not require a centrifugation step. This is extremely unwieldy from a manufacturing standpoint. By avoiding the need for a centrifugation step, the manufacturing process is greatly simplified, allowing for efficient scale up and for continuous manufacturing processing, as desired.

Furthermore, in Levy, the biologically active macromolecule is incorporated into the microspheres at the time of microsphere formation. In pending claims 43, 44 and 58-61, on the

other hand, the microparticle composition is incubated with a biologically active macromolecule after microparticle formation to adsorb the biologically active macromolecule to the microparticles in the composition. As noted above, by ensuring a process in which substantial detergent in the composition remains unbound to the microparticles, detergent is made available for forming a complex with the macromolecules at the time of adsorption. See, e.g., paragraph [0011] of the present specification.

With respect to cross-flow filtration in claim 36, the Office argues, apparently, along two lines: (I) Levy teaches washing. Cross-flow filtratration is equivalent to washing and is thus obvious in view of Levy. (II) Levy diclsoses filtration as a step, thus rendering obvious cross flow filtration. However, no evidence is provided in support of these conclusions. Washing particles in conjunction with centrifugation, as taught by Levy, doesn't remotely resemble cross-flow filtration. Moreover, washing and filtration are distinct concepts. See paragraph [0025] (emphasis added) ("no need for a filtration *or* washing step to remove excess detergent"). Furthermore, as noted above, centrifugation is not filtration. Levy does not teach or suggest a process in which microparticles are subjected to a filtration step, much less one which provides the claimed amounts of bound and unbound detergent.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143. Not one of these criteria has been met in the Office Action.

With respect to SDS, the Office has pointed to the disclosure of 0.1% SDS in Section 5.3.2. However, it appears that the Office has failed to recognize that Levy's use of SDS occurred after formation of DNA containing microspheres and that SDS was used to disrupt the microspheres in order to release entrapped DNA from the microspheres (see col. 19, ll. 8-13). In particular, at column 19, lines 8-10, Levy specifically teaches incubating DNA-containing microspheres in excess TE buffer with and without 0.1% SDS. At column 19, lines 11-13, Levy discloses that SDS was used to establish that charge-related associations between poly-L-lysine and DNA contribute to the DNA release and/or extraction mechanism. Thus, in Section 5.3.2, the SDS was used as an analytical reagent to release condensed DNA from the microspheres.

In contrast, in Applicants' claimed invention, detergent is used in a microparticle formation step. More specifically, detergent is included in step (a) of the independent claims, in forming an emulsion.

Paliard, which cited for its disclosure of CTAB as a detergent as claimed in claims 38 and 40, does not make up for the above noted deficiencies in Levy. For example, as elsewhere in the art at the time of the invention, washing is taught in Paliard in Example 5 (see col. 23, lines 53-55).

"The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP 2145.X.D.3. Citing *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

Furthermore, because the SDS was used as an analytical reagent in Levy as noted above, the Office's assertion that it would have been obvious to use the CTAB of Paliard in place of the SDS of Levy is not persuasive.

For at least the above reasons, it is respectfully submitted that the cited references do not support a *prima facie* case of obviousness against claims 34-44 and 58-67.

Reconsideration and withdrawal of the rejection of the claims under U.S.C. 103(a) as unpatentable over O'Hagan in view of Paliard are respectfully requested.

Claim Rejection under 35 U.S.C. 103-O'Hagan

Claims 34, 35, 36, 42 and 43 are rejected under 35 U.S.C. 103(a) as unpatentable over US 6,086,901 to O'Hagan et al. (O'Hagan). Applicant respectfully traverses this rejection and its supporting remarks.

As noted above, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See MPEP 2143. None of these criteria are met by the Office.

As also noted above, each of the independent claims in the present application, including claim 34, requires either (I) that the microparticles are subjected to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the

microparticles and the remainder is unbound or (II) that the microparticles are not subjected to a washing step and the ratio of the detergent to the polymer used is such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

With respect to limitation (II), O'Hagan describes washing and centrifugation, as do Levy and Paliard above. See, for instance, Example 1, col. 14, lines 62-63 (washed three times using centrifugation) and Example 3, col. 16, lines 3-4 (also washed three times using centrifugation). Again, as noted in paragraph [0011] of the specification, techniques in which microparticles are washed multiple times with water, such as the process of O'Hagan, remove essentially all unbound detergent, resulting in a final product in which greater than 99% of the remaining detergent is bound to the particles.

With respect to limitation (I), O'Hagan does not teach or suggest a filtration step that would provide bound and unbound detergent in the amounts claimed. This is even more clearly apparent with respect to the cross-flow filtration step claimed in claim 36. In this regard, although the Office correctly notes that O'Hagan discloses washing (as pointed out in the prior paragraph), the Office is incorrect in its assessment that cross-flow filtration "reads on washing" because it "appears to approximate the process of filtration/washing." Washing and filtration are distinct concepts, and the disclosure of washing in a reference does not render filtration obvious (for example, washing in O'Hagan is conducted in conjunction with centrifugation), particularly a specific filtration technique such as the filtration technique described in claim 36. Finally, as pointed out above, techniques in which microparticles are washed multiple times with water, such as the process of O'Hagan, remove essentially all unbound detergent. In the present claims, on the other hand, microparticles are subjected to a filtration step such that about 10-90% of the total detergent in the microparticle composition is bound to the microparticles. No such step is taught or suggested by O'Hagan.

The Office urges that O'Hagan does not teach *against* producing particles that have substantial amount of unbound detergent. It is, however, not seen how this is relevant to the issue of obviousness. What *is* relevant is that O'Hagan does not teach or suggest processes like those presently claimed, which yield microparticle compositions in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound.

For at least these reasons, it is believed that claim 34, as well as claims 35, 36, 42 and 43 depending therefrom, are patentable over O'Hagan. Reconsideration and withdrawal of the rejection of these claims over O'Hagan are respectfully requested.

CONCLUSION

Applicants submit that the claims of the present invention are in condition for allowance, early notification of which is earnestly solicited. Should the Examiner be of the view that an interview would expedite consideration of this Amendment or of the application at large, request is made that the Examiner telephone the Applicant's attorney at (703) 433-0510 to resolve any outstanding issues.

FEES

The Office is authorized to charge any additional fees required to deposit account number 50-1047.

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(Signature)

Hawley's

Condensed Chemical Dictionary

Fourteenth Edition

Revised by

Richard J. Lewis, Sr.

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sten, gold) or a metal carbide.
See fiber.

filament winding. The process of winding fibers under tension onto a prepared core. Before or during the winding operation, the assembly is impregnated with a thermosetting resin. Structures of considerable size and strength can be made in this way. The fibers used are chiefly glass, boron, or silicon carbide.
See filament.

filler. (1) An inert mineral powder of rather high specific gravity (2.00–4.50) used in plastic products and rubber mix to provide a certain degree of stiffness and hardness and to decrease cost. Examples are calcium carbonate (whiting), barytes, blanc fixe, silicates, glass spheres and bubbles, slate flour, soft clays, etc. Fillers have neither reinforcing nor coloring properties, and the term should not be applied to materials that do, i.e., reinforcing agents or pigments. Fillers are similar to extenders and diluents in their cost-reducing function; exact lines of distinction between these terms are difficult, if not impossible, to draw. Use of fillers and extenders in plastics has increased in recent years due to shortages of basic materials.
(2) The cross or transverse thread in a fabric or other textile structure.
(3) A metal or alloy used in brazing and soldering to effect union of the metals being joined. See diluent; extender; reinforcing agent.

film. An extremely thin continuous sheet of a substance that may or may not be in contact with a substrate. There is no precise upper limit of thickness, but a reasonable assumption is 0.010 inch. The protective value of any film depends on its being 100% continuous, i.e., without holes or cracks, since it must form an efficient barrier to molecules of atmospheric water vapor, oxygen, etc. A long-chain fatty acid or alcohol on water produces a film whose thickness is the length of one molecule (approximately 200 Å). The fatty acid molecules are oriented with the radical end in the water. Such films are good evaporation barriers and have been successfully imposed on glass. Soap bubbles are elastic films about one micron thick and have considerable strength. Film-forming agents (drying oils) are essential in paints and lacquers. Oxide films formed automatically on the surface of aluminum protect it from corrosion. Thin metallic oxide films are widely used in electronic and semiconducting devices. Electrodeposited metals (chromium, copper, nickel) are conventionally (and perhaps illogically) called coatings. The term film is also applied to sheets of cellophane, polyethylene, polyvinylidene chloride, etc., used for wrapping and packaging of food products, meats, and poultry (especially shrink films that are stretched before application). These function as a moisture vapor barrier. Plastic films are also used as slip surfaces in concrete structures such as airstrips, ice rinks, and highways. Photographic film is made from cellulose acetate.

filter. See filtration; leaf, filter; baghouse.

filter aid. See filter media; filtration.

filter alum. See aluminum sulfate.

filter medium. Almost any water-insoluble, porous material having a reasonable degree of rigidity can serve as a filter. Sand is used in simple large-scale water filtration, the voids between the grains providing the porosity. In industrial operations, cotton duck, woven wire cloth, nylon cloth, and glass cloth are used. For laboratory work, Whatman filter paper, diatomaceous earth, and closely packed glass fibers are standard materials. Plastics membranes containing more than a million pores per square inch are used in bacteriological filtration.
See filtration; screen.

filter sand. Sand used to separate sediment and suspended matter from water.

filtration. The operation of separating suspended solids from a liquid (or gas) by forcing the mixture through a porous barrier (see filter media). The construction and operation of the many kinds of industrial filtration equipment are too detailed to permit description. The most widely used types may be classified as follows: (1) gravity filters, used largely for water purification and consisting of thick beds of sand and gravel that retain the flocculated impurities as the water passes through (2) pressure filters of plate-and-frame or shell-and-leaf construction that utilize filter cloths of coarse fabric as a separating medium; (3) vacuum or suction filters of the rotating drum or disk type, used on thick sludges and slurries; (4) edge filters; (5) clarification filters; (6) bag filters (dust collectors). Gel filtration is a chromatographic technique involving separation at the molecular level. For bacteriological filtration, membranes having more than a million pores per square inch are used, e.g., collodion or synthetic film. Some types of viruses will pass through such membranes and are thus known as filterable viruses.
See baghouse.

fine chemical. A chemical produced in comparatively small quantities and in a relatively pure state. Examples are pharmaceutical and biological products, perfumes, photographic chemicals, and reagent chemicals.

fines. The portion of a powder composed of particles that are smaller than a specified size (MPA definition, MPA Standard 9–50T).

finishing compounds. Materials that impart softness, flexibility, stiffness, color, water and fire resistance, etc.